Peter Theunissen; NVT Pharmaceutical Toxicology Section Symposium
18 April 2023

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EVALUATION
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New Regulatory Opportunities in DART

For Pharmaceutcal Development

GOOD MEDICINES USED BETTER

A Short History of DART testing

<u>Thalidomide (softenon in NL)</u>

- Late 1950’s on the market as drug against morning sickness
- Caused impaired limb growth in human embryo’s (Phocomelia)
- Increased awareness of possible effects of drugs and chemicals on embryonic development

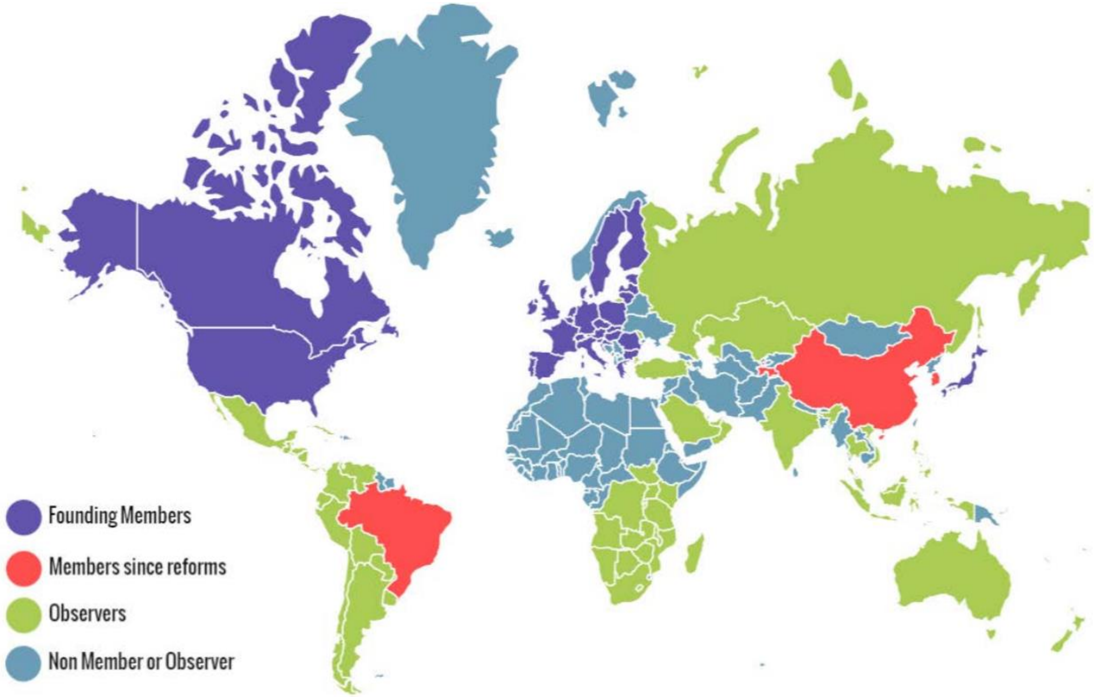
Thalidomide tragedy led to safety guidance for DART testing:

→1970s first guidelines for reproductive toxicity testing for medicines (FDA)

→in 1980s for chemicals (OECD)

→Global Harmonized DART Guideline for Pharmaceuticals in 1995 (ICH S5)

Current DART guidance for Pharmaceuticals: ICH S5(R3)



ICH
harmonisation for better health

INTERNATIONAL COUNCIL FOR HARMONISATION OF TECHNICAL REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED GUIDELINE

DETECTION OF REPRODUCTIVE AND DEVELOPMENTAL TOXICITY FOR HUMAN PHARMACEUTICALS

S5(R3)

Final version
Adopted on 18 February 2020

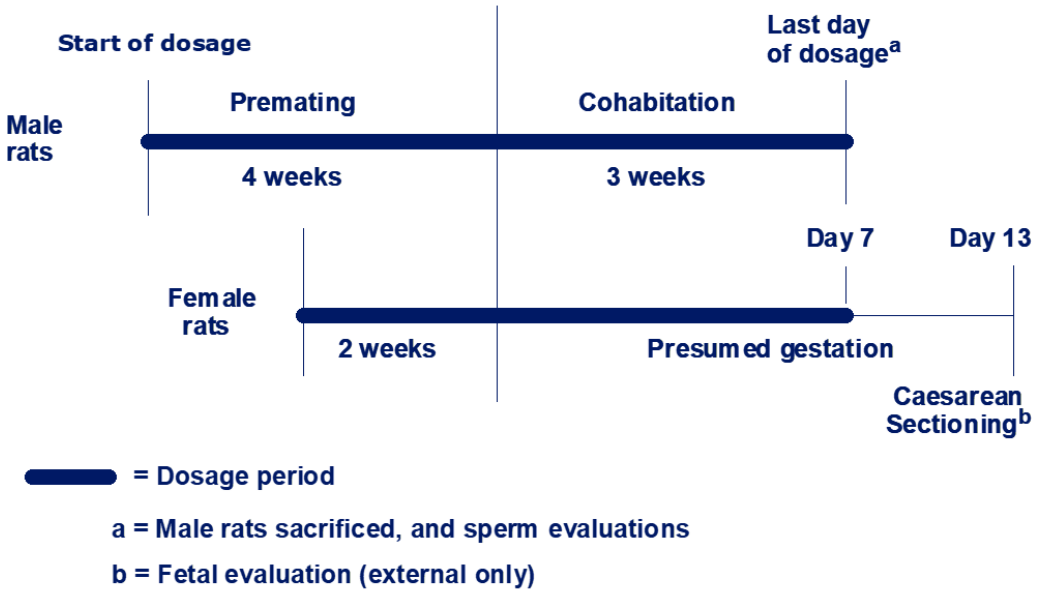
Default DART testing under ICHS5(R3)

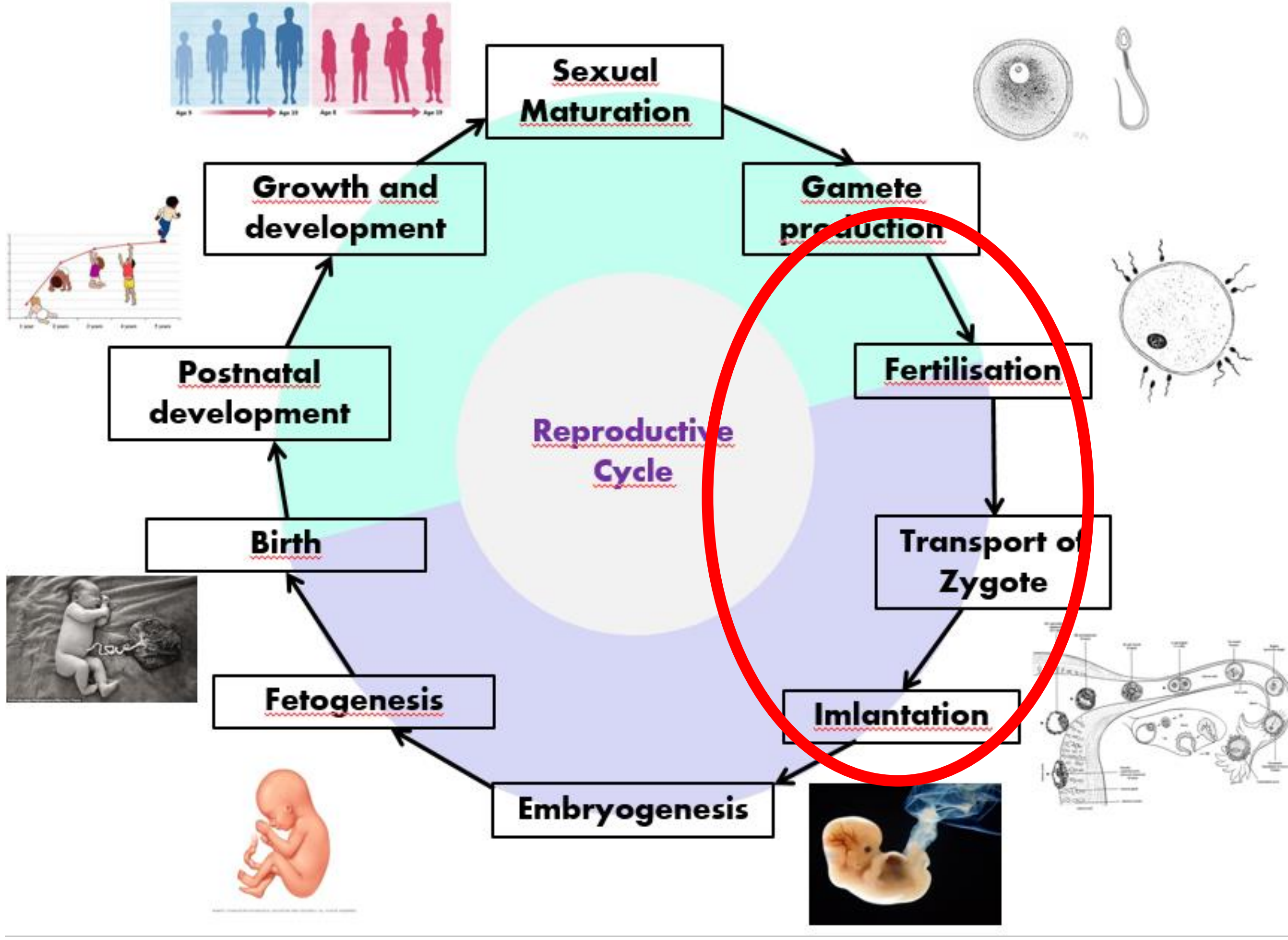
Effects of pharmaceuticals on reproductive cycle

Fertility and Early Embryonic Development (FEED)

Toxicity study

→ 2-4 weeks before conception – implantation





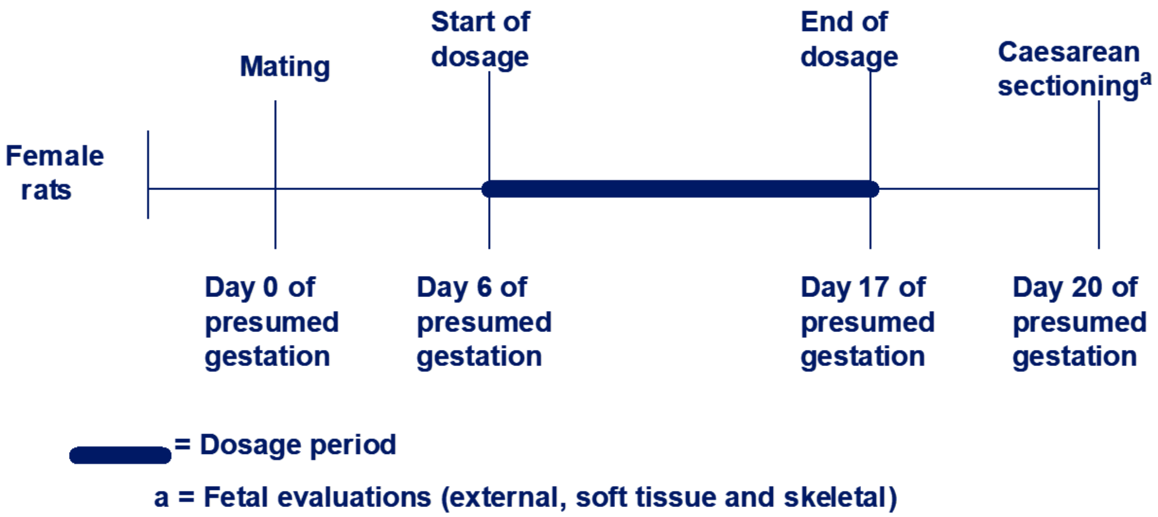
Default DART testing under ICHS5(R3)

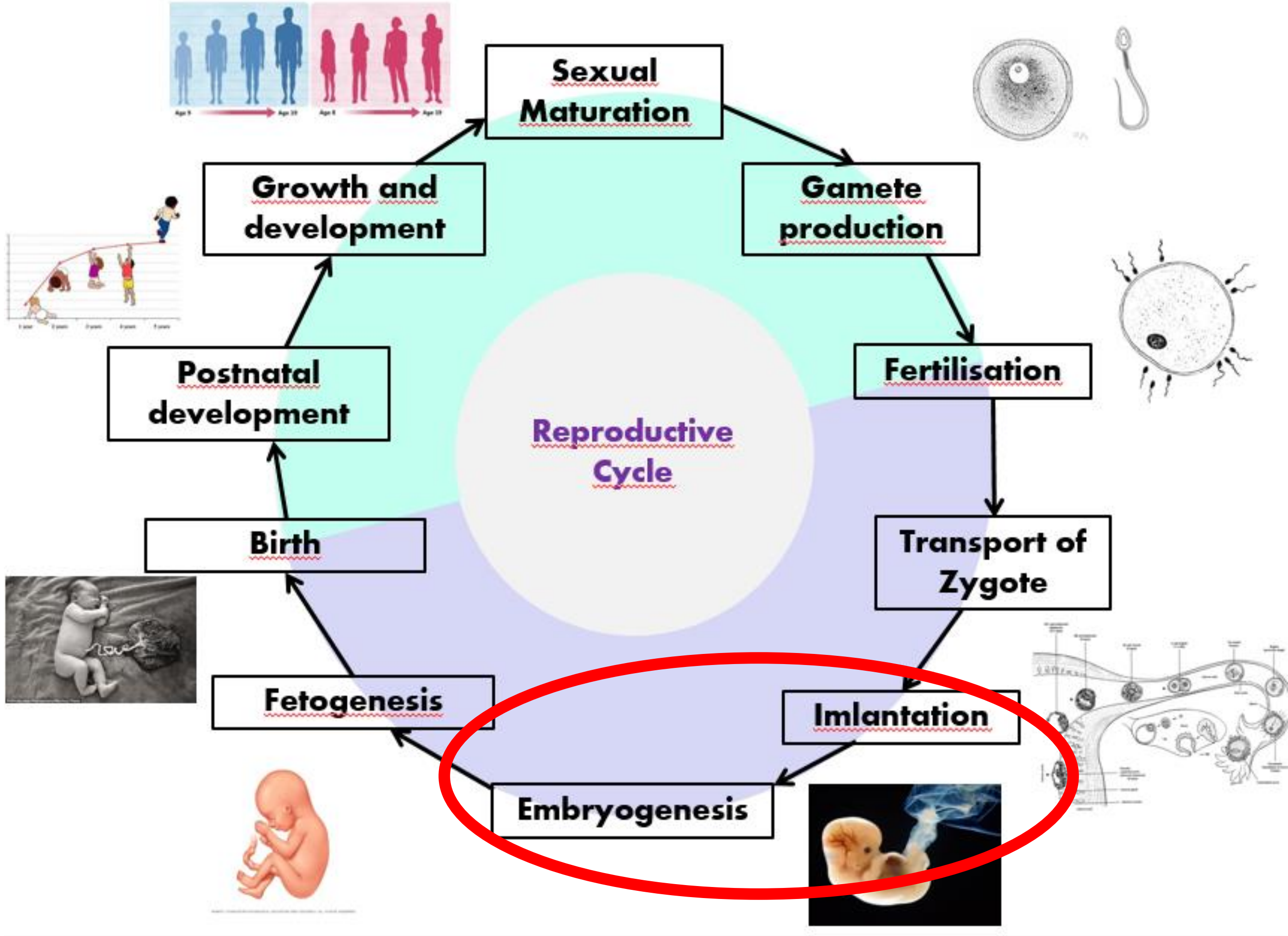
Effects of pharmaceuticals on reproductive cycle

Embryo-fetal Developmental (EFD) Toxicity study

→ Implantation – closure of hard palate

→ Default 2 species (rodent and non-rodent)





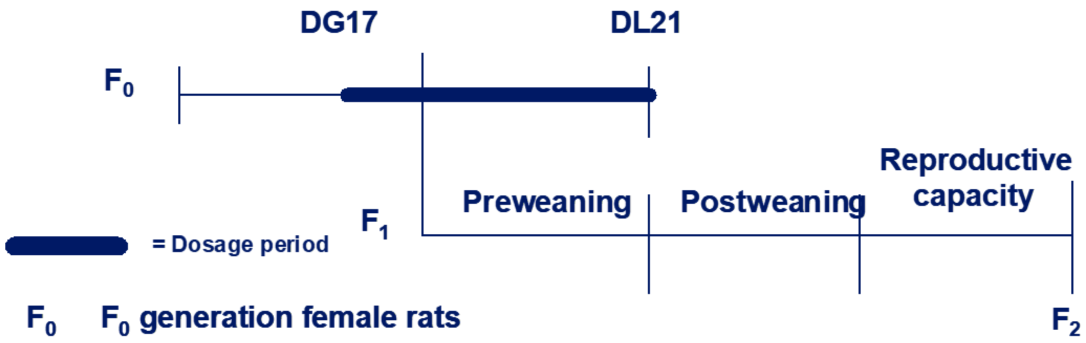
Default DART testing under ICHS5(R3)

Effects of pharmaceuticals on reproductive cycle

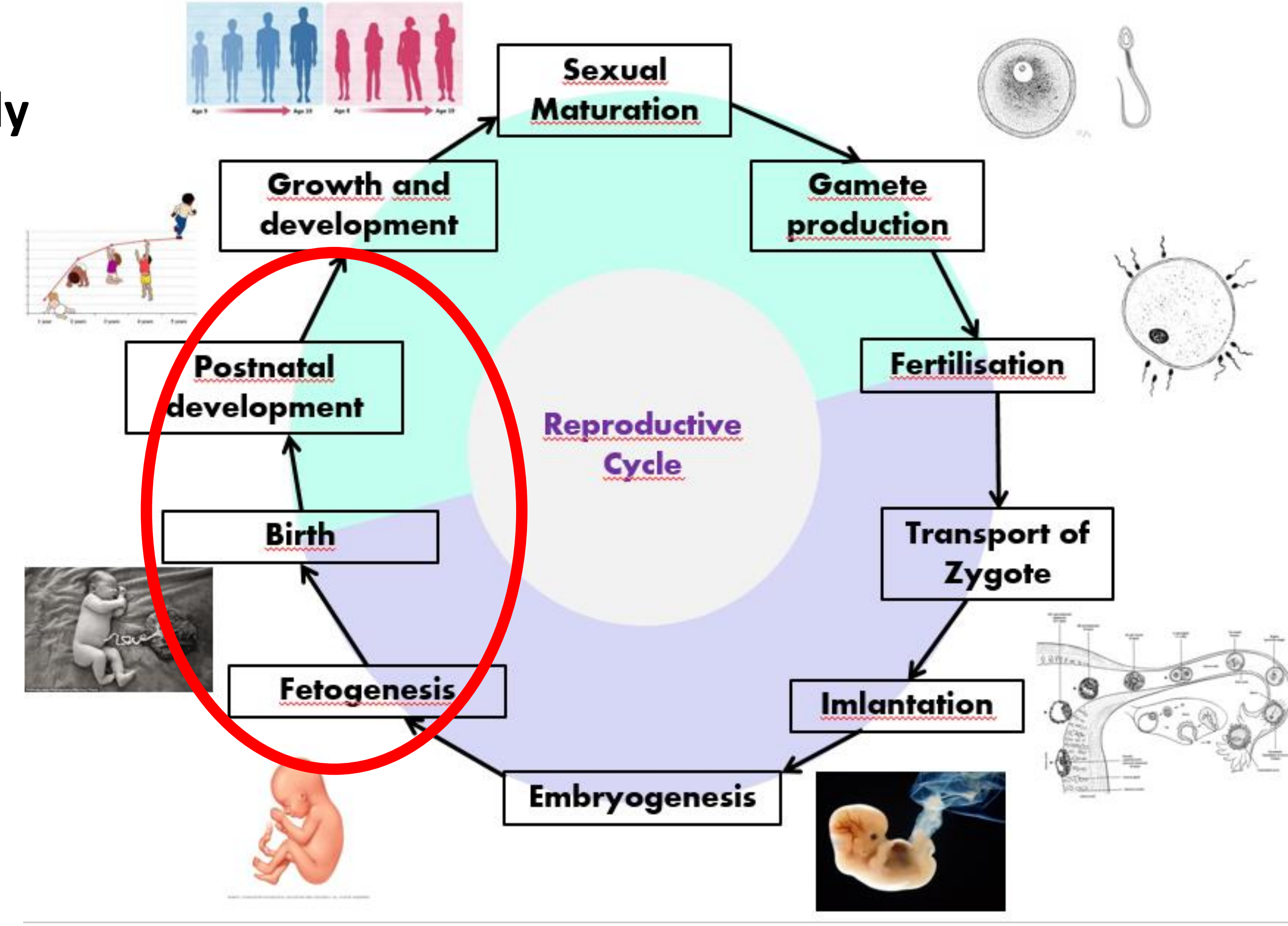
Pre-post Natal Developmental (PPND) Toxicity study

→ closure of hard palate - weaning

- → Optional start at implantation
- → Optional up to F1 generation



F_0	F_0 generation female rats
F_1	F_1 generation (offspring of F_0 generation)
F_2	F_2 generation (offspring of F_1 generation)
DG	Day of gestation
DL	Day of lactation



New Approach Methods (NAMs) for EFD toxicity testing (history)

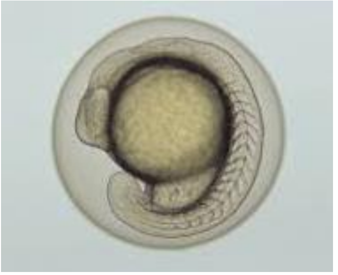
Classic models

Whole Embryo Culture (WEC) (1970s)

Embryonic Stem Cell Test (EST) (1990s)

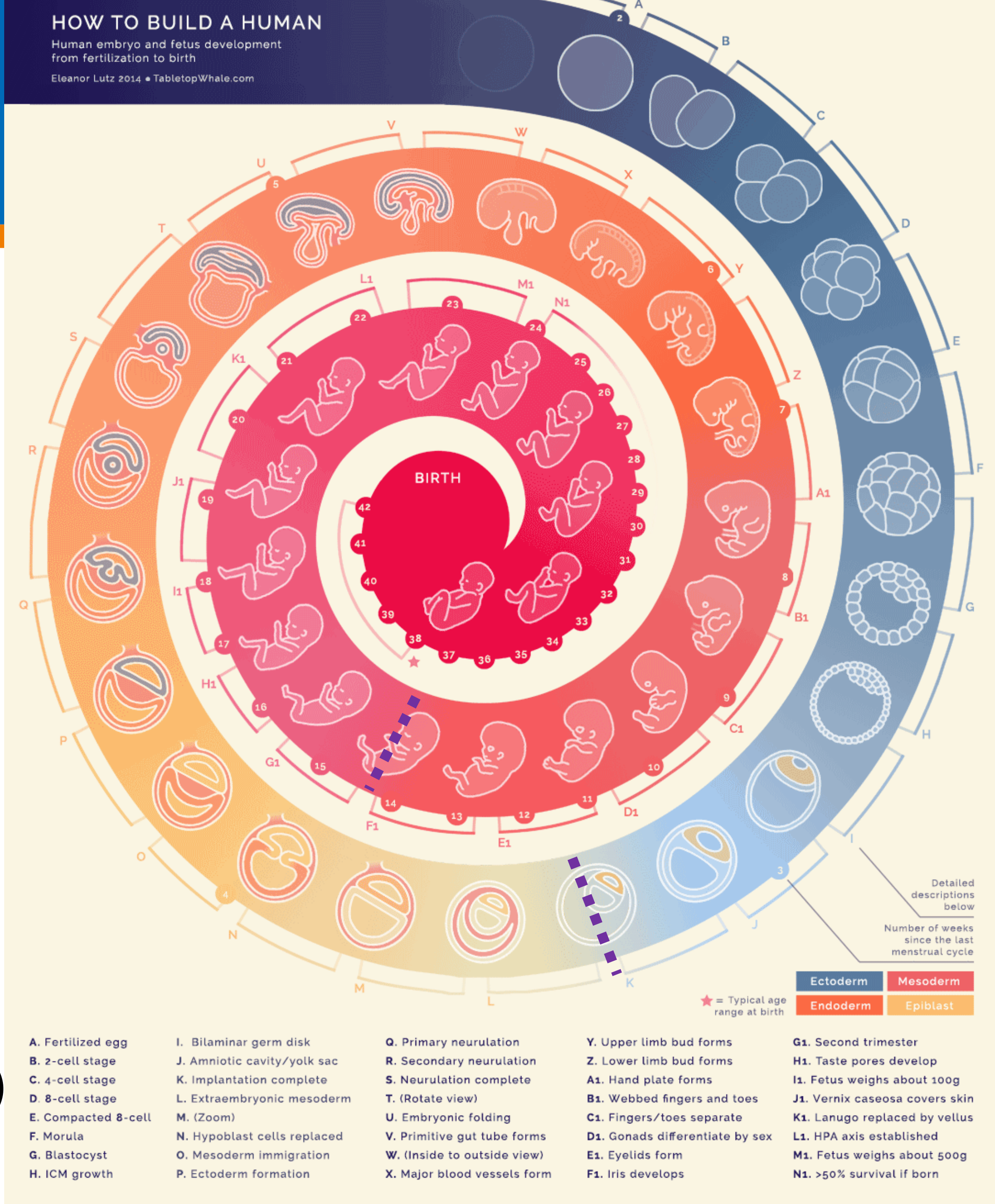
Zebrafish Embryo Toxicity Test (ZET) (2000s)

Aart Verhoef, RIVM



Sanne Hermsen, RIVM

- Investigate effects on development during window of implantation – closure hard palate
- Endpoints based on morphology
- Validation effort by ECVAM WEC/cardiac EST (2004-2009)



NAMs and innovation; Fast moving field!

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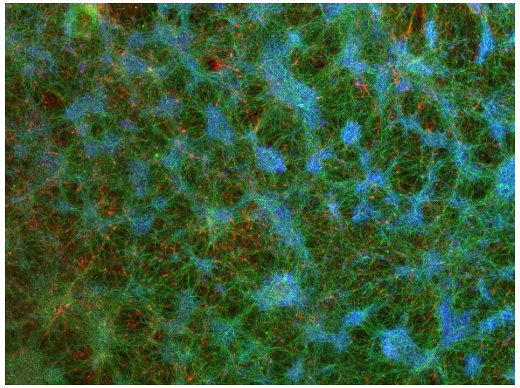
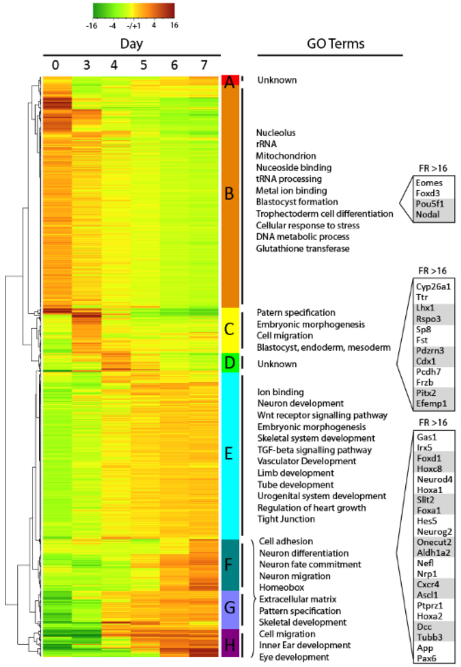
Imaging

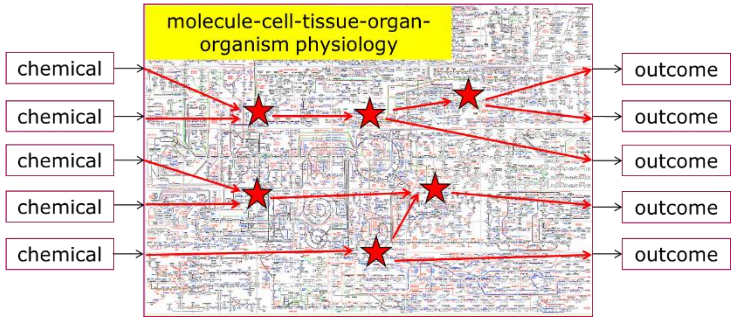


De Leeuw, 2020

PCR / OMICS

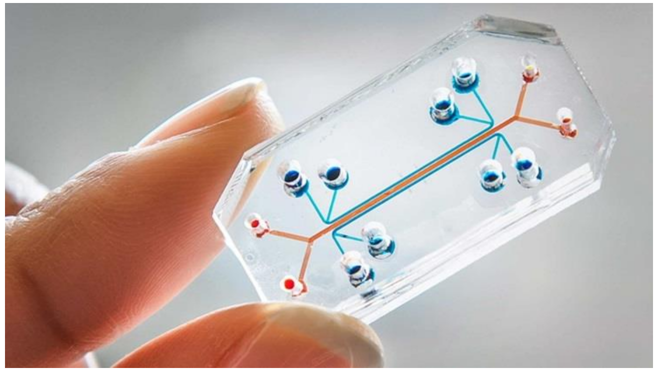


AOPs

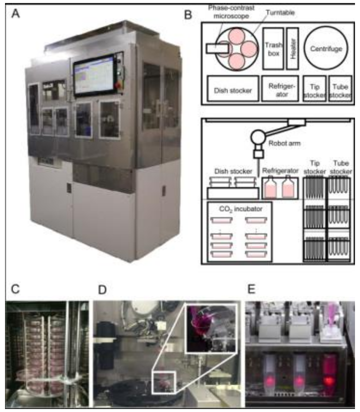


Aldert Piersma, RIVM

Organ on Chip

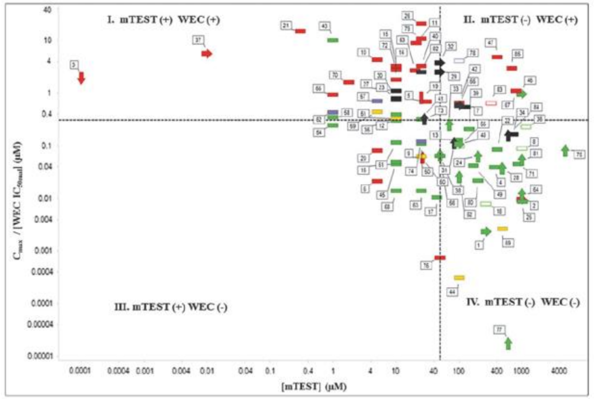


Robotics



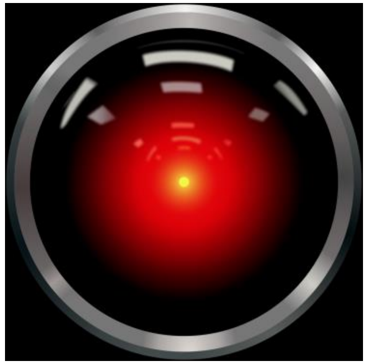
Konagaya, 2015

Tiered approach Testing Batteries



Green, 2018

Machine Learning / Artificial Intelligence



NAMs under ICH S5 (1995-2020); Changing regulation is very slow … … …

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ICH Topic S 5 (R2)
Detection of Toxicity to Reproduction for Medicinal Products & Toxicity to Male Fertility

Step 5

NOTE FOR GUIDANCE ON THE DETECTION OF TOXICITY TO REPRODUCTION FOR MEDICINAL PRODUCTS & TOXICITY TO MALE FERTILITY
(CPMP/ICH/386/95)

2.2. Other test systems

Other test systems are considered to be any developing mammalian and non-mammalian cell systems, tissues, organs, or organism cultures developing independently in vitro or in vivo. Integrated with whole animal studies either for priority selection within homologous series or as secondary investigations to elucidate mechanisms of action, these systems can provide invaluable information and, indirectly, reduce the numbers of animals used in experimentation. However, they lack the complexity of the developmental processes and the dynamic interchange between the maternal and the developing organisms. These systems cannot provide assurance of the **absence** of effect nor provide perspective in respect of risk/exposure. In short, there are no alternative test systems to whole animals currently available for reproduction toxicity testing with the aims set out in the introduction (Note 6).

NAMs under ICHS5(R3) (2020-present)

2010 Start of preparatory process at ICH level

2015 Official start of Revision procedure

2019 Step 4 approval by ICH

2020 Step 5 regional implementation

First ICH guidance to include information on use and qualfication of NAMs as alternative for EFD testing

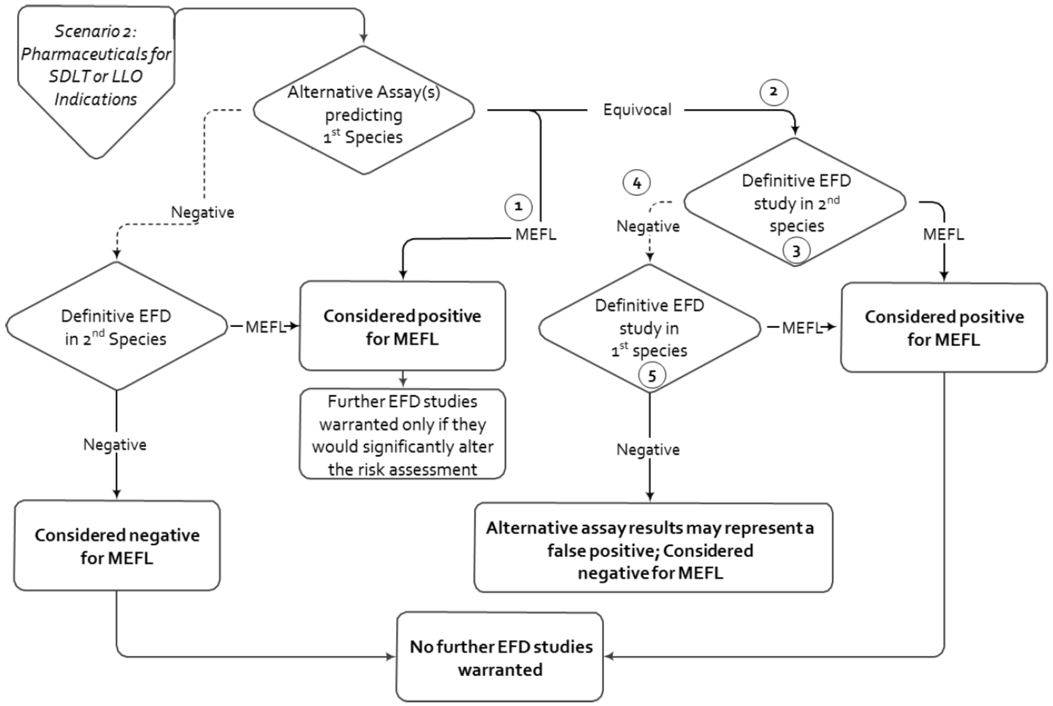
Because science develops quickly,
and regulation does NOT… →

All information on NAMs and qualification in ANNEX → ICHS5(R4) maintenance procedure
- Possibility for 2 yearly changes to Annex

When to USE NAMs under ICHS5(R3)

- To support Phase I + II clinical trials (=saving animals by attrition)
- **Qualified** alternative assays (predict **MEFL*** outcome in first species) + pEFD in a second species
- **Rodent** and **non-rodent** should be covered,
- Enable the limited inclusion of WOCBP (up to **150 WOCBP for up to 3 months**).

- Known **MoA** (class effects, known effect on developmental pathways) (ICHS5(R3)scheme figure 1 Annex 2, p39)
- No clinically relevant **exposure** possible in animals
- Support for WoE assessment when **equivocal** results in animal studies
- Indication for **severely debilitating** or **life-threatening diseases or late-life onset diseases**



ICHS5(R3) figure 2 Annex 2, p39

*MEFL = malformations and embryo-fetal lethality

How to QUALIFY NAMs under ICHS5(R3) (1/2)

Under ICHS5(R3), NAMs approaches should:

- provide a level of **confidence** for human safety assurance at least equivalent to that provided by the current testing paradigms.
- be **qualified** within a **certain context of use**, defined by
  - the **chemical applicability domain** of the assay, and
  - characterization of the **biological mechanisms** covered by the assay.

How to QUALIFY NAMs under ICHS5(R3) (2/2)

Qualification Criteria (ICHS5(R3), p36-37):

- Description and justification of predictive model
  - Which species does it predict Malformations and Embryo-fetal lethality (MEFL) for?
- Evaluation of biological plausibility of the model,
  - Mechanism of embryonic development in the model + adverse effects
  - Limitations of the models
  - Developmental window of prediction (in vivo)
- Determination of endpoints, and when negative or positive
- Statistical evidence to predict MEFL in a species (accuracy, prediction, sensitivity, specificity etc.)
- Historical data of the test system
- Reference compounds
  - list of training sets / test sets, source of data
  - Description of chemical domain predicted

Reference compound list for NAMs under ICHS5(R3)

29 example Reference Compounds are listed in Annex II and published by Andrews et al, 2019.

Contents lists available at ScienceDirect

Regulatory Toxicology and Pharmacology

journal homepage: www.elsevier.com/locate/yrtph

Analysis of exposure margins in developmental toxicity studies for detection of human teratogens

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[h] CBG-MEB, Utrecht, the Netherlands

Positive Controls	Human Teratogen	Rat MEFL	Rabbit MEFL
Acitretin	X	X	X
Aspirin	X	X	
Bosentan		X	
Busulfan	X	X	X
Carbamazepine	X	X	X
Cisplatin		X	
Cyclophosphamide	X	X	X
Cytarabine	X	X	
Dabrafenib		X	
Dasatinib		X	
Fluconazole	X	X	X
5-Fluorouracil	X	X	X
Hydroxyurea	X	X	X
Ibrutinib		X	X
Ibuprofen	X	X	
Imatinib		X	
Isotretinoin (13-*cis*-retinoic acid)	X	X	X
Methotrexate	X	X	X
Pazopanib		X	X
Phenytoin (Diphenylhydantoin)	X	X	X
Pomalidomide	presumed	X	X
Ribavirin		X	X
Tacrolimus		X	X
Thalidomide	X	X	X
Topiramate	X	X	X
Tretinoin (all-*trans*-retinoic acid)	X	X	X
Trimethadione	X	X	
Valproic acid	X	X	X
Vismodegib	presumed	X	

Cyclophosphamide

CAS No.: 50-18-0

Rat NOAEL **Dose** C_{max} **AUC**	**Rat LOAEL** **Dose** C_{max} **AUC**	**Rat Findings**	**Rabbit NOAEL** **Dose** C_{max} **AUC**	**Rabbit LOAEL Dose** C_{max} **AUC**	**Rabbit Findings**	**Human** **Dose** C_{max} **AUC**	**Margins** **NOAEL/Huma** **LOAEL/Human**	**Notes**
NOAEL not identified (<2.5 mg/kg) [Chaube]	2.5 mg/kg IP GD9 [Chaube] Cytoxan C_{max} = 4.1 μg/mL[a] AUC = 3.65 μg·h/mL[a] PM C_{max} = 0.55 μg/mL[b] $AUC_{(0\text{-}24h)}$ = 2.13 μg·h/mL[b]	2.5 mg/kg GD9 [Chaube] embryolethal 5 mg/kg GD11 [von Kreybig, Mirkes] encephalocele, exencephaly, microcephaly, limb defects (ie, syndactyly and ectrodactyly), defective facial development (cleft palate)	NOAEL not identified (<30 mg/kg)	30 mg/kg IV single doses on GD6-14 [Mirkes, Fritz] Cytoxan C_{max} = 151 μg/mL[c] $AUC_{(0\text{-}8h)}$ = 24.1 μg·h/mL[d] PM C_{max} = 0.07 μg/mL[e] $AUC_{(0\text{-}8h)}$ = 0.297 μg·h/mL[e]	embryo-fetal resportions, omphalocele, cleft lip/ palate, forelimb skeletal defects	1600 mg/m^2 (40 mg/kg) IV (highest dose, q 3 – 4 weeks)[f] Cytoxan C_{max} = 106 μg/mL[g] AUC = 798 μg·h/mL[g] PM C_{max} = 14.4 μg/mL[h] AUC = 352 μg·h/mL[h]	NOAEL: rat: NOAEL not identified, but LOAEL margins were <0.1 rabbit NOAEL not identified, but LOAEL margins were <1.5 LOAEL: rat C_{max}: 0.04 (4.1/106) AUC: 0.005 (3.65/798)	• MW CP = 261.086 • MW PM = 221.018 • Cytoxan is a prodrug, MEFL has been attributed to both phosphoramide mustard (PM) and acrolein metabolites

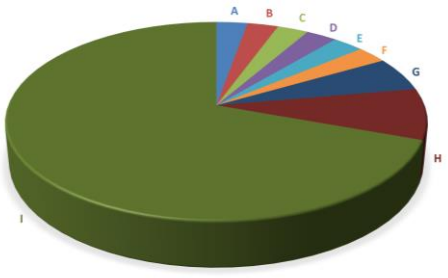
Regulatory state of ICHS5(R3)

Since implementation of ICHS5(R3)

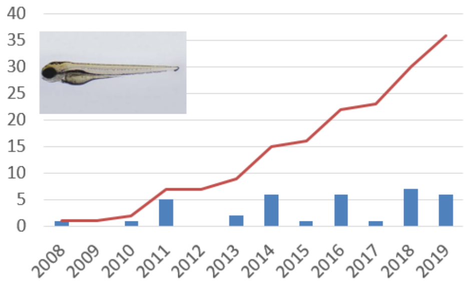
- No qualification exercises started at EMA
- One interested party at FDA, but not pursued further

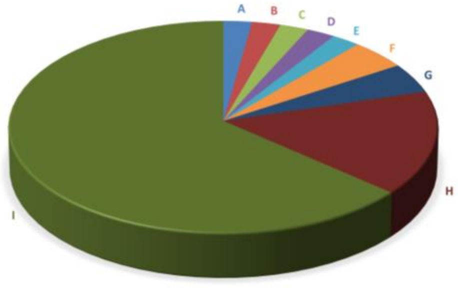
Companies do generate data in house (60% of responders to IQ survey, not published)

Sometimes shared through submissions

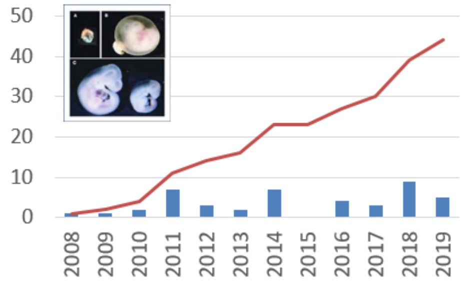


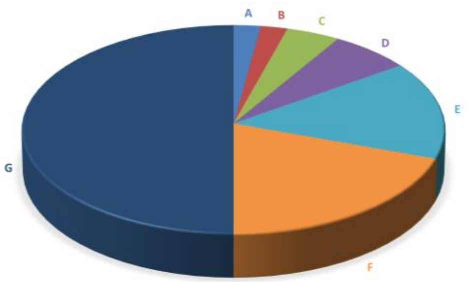
Zebrafish



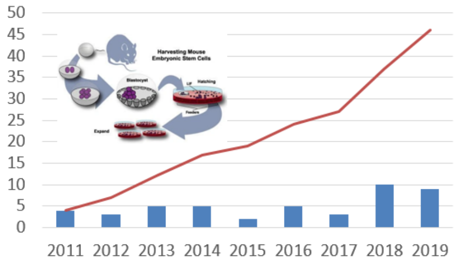


Whole Embryo Culture





Embryonic Stem Cells



Companies are uncertain about qualification: what is expected, consequences

Regulators need to get more experienced with NAMs for regulatory purposes

IMPASSE…

Figures kindly provided by Ronald Wange, FDA

Breaking the Impasse and get Qualification moving at EMA

EMA wants to kickstart the Qualification of NAMs

3RsWorking Party restarted in 2022

- Updating and new **guidance** on qualification
- **Support** for qualification applications
- European Specialised Expert Community (**ESEC**) for NAMs
- Creation of a **worldwide cluster** of regulators for global alignment

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Innovative Task Force (**ITF**)

- **Informal** talks with EMA experts and ESEC members
- Discuss **proof of concept** and possibilities for qualification
- **Free** of charge

Formal talks with EMA before qualification (3RsWP / SAWP advice)

Formal Qualification (SAWP qualification advice)

→ EMA **certificate** that NAMs can be used under a certain context of use.

Future of NAMs in DART testing

- Find common ground with industry to start qualifications →
- Increase in Qualification applications →
- Increased regulatory experience →
- More scenarios in which NAMs can be used under ICHS5(R3) Annex II

- Obtain more human relevant mechanistic data
- Decreased use of test animals
- Increased relevance for Labeling for Pregnant women, Lactation and Fertility

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